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Original Research Article

COMPARATIVE STUDY OF THE ANTINOCICEPTIVE EFFECTS OF GABAPENTIN ALONE AND A COMBINATION OF GABAPENTIN AND VITAMIN C IN PATIENTS SUFFERING FROM NEUROPATHIC PAIN

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Abstract

Background: Neuropathic pain (NP) is an underestimated socioeconomic health problem affecting millions of people worldwide. Gabapentinoids with vitamin C are now considered to be treatment for post-SCI neuropathic pain, mimic the neurotransmitter GABA and show indirect interaction with the GABA receptor. The aim of this study was to investigate whether VitC can enhance the analgesic effect of gabapentin in neuropathic pain in humans and the possible mechanism behind such an effect. **Materials and Method:** A hospital based observational study was conducted in 60 patients of diagnosed neuropathic / nociceptive and neuropathic pain in Muzaffarnagar Medical College & Hospital, Muzaffarnagar, Uttar Pradesh. There were 2 study groups (group A: who received only gabapentin and group B: who received both gabapentin and vitC). Study was conducted for 18 months. Data was analyzed statistically using mean, standard deviation and SPSS 22. **Result:** The participants in this study ranged from 18-60 years old. There was statistically significant difference between the two study groups in terms of NRS scale. There were less adverse effects noted in group B although no statistically significant difference was noted among the groups. **Conclusion:** We finally concluded that the addition of vitC to gabapentin in the treatment of patients with neuropathic pain actually helped in improving the efficacy of the drug and improved the quality of life of the patients.

INTRODUCTION

One of the most persistent problems in medical history is the endeavor to comprehend pain. Pain serves as the quintessential symptom and is, therefore, a powerful and significant tool in medical activity.[1] Pain can be caused by nerve damage or by the nociceptive pathways becoming activated after tissue damage. Disrupted motor signals returning to the limb after disturbed sensory system inputs appear to cause a mismatch between the brain's internal picture of the body and what is actually observed. Pain arises from this mismatch for some reason.[2]

Neuropathic pain (NP) is currently a socioeconomic health issue that is underappreciated and affects millions of individuals globally. It has been recently redefined by the International Association for the Study of Pain as a 'pain caused by lesion or disease of the somatosensory system" and it may appear in a wide range of conditions; it can be classified into peripheral or central NP, depending on the anatomic location of the lesion or disease. It is an indicator of disorganized motor and sensory reference frames that an evolved adaptive system in the central nervous system responds to as an indication of non-specific trauma.[3,4]

There may be many causes of NP, but some common causes of neuropathic pain include diabetes (painful diabetic neuropathy (PDN)), shingles (postherpetic neuralgia (PHN)), amputation (stump and phantom limb pain), neuropathic pain after surgery or trauma, stroke or spinal cord injury, trigeminal neuralgia, and HIV infection. Sometimes the cause is unknown.[5]

The recommended first-line treatments for neuropathic pain include antidepressants (tricyclic antidepressants and dual reuptake inhibitors of both serotonin and norepinephrine), calcium channel α2d ligands (gabapentin and pregabalin) and topical

lidocaine. Opioid analgesics and tramadol are generally recommended as second-line treatments that may be considered for first-line use in selected clinical circumstances. Other medications that are generally used as third-line treatments (may be used as second-line treatments in some circumstances) are other antiepileptic and antidepressant medications, mexiletine, N-methyl-D aspartate receptor antagonists and topical capsaicin.[6,7]

Gabapentin (Gap) is licensed for the treatment of peripheral and central neuropathic pain. It is given orally, usually as tablets or capsules, but sometimes as an oral solution (50 mg/ml).[8] Gap, which is also used as an antiepileptic drug, has a number of side-effects such as dizziness, ataxia, peripheral edema, and confusion, especially at higher doses.[9-12]

Previous studies have shown that ROS can mediate the occurrence and maintenance of neuropathic pain, while free radical scavengers can relieve neuropathic pain. Vitamin C (VitC) is an antioxidant that can scavenge ROS by losing 2 electrons and transform into de-hydro ascorbate (DHA). There have been published reports about the analgesic effect of Vit C in both animals and humans with neurogenic pain.[13-15] Vitamin C can thus be regarded as a safe and effective adjuvant in the treatment of acute and chronic pain in a certain group of patients.

Based on such studies, we hypothesized that Vit C might enhance the analgesic effect of gabapentin, thus reducing the required dose and associated side effects of gabapentin in neuropathic pain. The aim of this study was to investigate whether VitC can enhance the analgesic effect of gabapentin in neuropathic pain in humans and the possible mechanism behind such an effect.

MATERIALS AND METHOD

The present hospital based observational study was conducted at Pain clinic in the Department of Anaesthesiology and Critical Care, Muzaffarnagar Medical College for a period of 18 months among cases of chronic pain (neuropathic pain / nociceptive and neuropathic) visiting OPD. Ethical clearance was taken from institutional ethics committee before commencement of study. A written informed consent was taken from each patient or his/her legally authorised relative after explaining the research protocol and all the possible complications related to the treatment protocol in the language patient understands.

Primary sample size was decided with consultation of statistician and was based in order to detect type 1 error of 0.01 and power of 90%, which indicated that approximately 27 patients should be included in each group. Assuming a 5% dropout rate, the final sample size was set at 30 patients in each group. Each and every patient of neuropathic pain will be selected in the study based on inclusion criterias.

Inclusion Criteria

After approval from institutional ethical committee, patients included in our study were-

1. Clinically diagnosed patients of neuropathic pain (DN-4 scale).
2. Of both sexes.
3. Between the age groups of 18-60.
4. With no uncontrolled severe comorbidities, despite taking regular medications (ASA grades I and II).

Exclusion Criteria

Patients excluded were those-

1. Not willing for procedure.
2. Below the age of 18 years and/or above 60 years.
3. With nociceptive pain of any other cause.
4. With a known sensitivity to the study drugs.
5. With psychiatric illness.

Randomization: The total adult consented 60 patients were randomized into two groups of 60 patients each using computer generated randomized tables.

Group A (n = 30): Patients received gabapentin in the dosage of 10 mg/kg.

Group B (n = 30): Patients received gabapentin (10mg/kg) and vitamin c in the dosage of 10 mg/kg as an adjunct to gabapentin.

Methodology: Written and informed consent was taken for inclusion in study. Randomization was then done through computer generated table and the patients were divided into two groups i.e. A and B as mentioned above. A detailed history of every patient along with the complaints, duration of illness, family history was taken. General physical examination and systemic examination was conducted. Neuropathic pain was confirmed in patients using DN-4 criteria. Group A patients were prescribed only gabapentin in the dosage of 10 mg/kg and group B patients were prescribed gabapentin (10mg/kg) and vitamin C in the dosage of 10 mg/kg as an adjunct to gabapentin. Both the groups A and B were followed up every 15 days for a period of 3 months. Response was assessed on the percentage of reduction in pain based on numerical rating scale (NRS) of 0-10: 0: None, 1-3: Mild pain, 4-6: Moderate pain and 7-10: Severe pain. The results were evaluated after 30 days and last follow up from the baseline. Data was collected and subjected to statistical analysis.

Statistical Analysis: Data so collected was tabulated in an excel sheet, under the guidance of statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA). Difference between two groups was determined using t-test as well as chi square test and the level of significance was set at $p < 0.05$.

RESULT

The subjects were of different age groups such as between 18-30, 31-40, 41-50 and > 50. However maximum subjects were from age group of >50 years (40% in group A and 53.33% in group B) followed by 41-50 year age group and so on. Minimum subjects were from age group of 18-30 years. When

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age distribution was compared among the study groups, no significant difference was found between the two groups as the p-value was > 0.05. Males were 17 in number in group A and 18 in group B. Females on the other hand were 12 and 13 in respective groups. The p-value came out to be 0.72 (more than 0.05) thus making the difference between both the groups statistically non-significant as shown in [Table 1].

BMI in group A and B was 27.01±4.24 and 27.69±3.93 kg/m2 respectively with statistically insignificant difference. The p-value being > 0.05 as shown in [Table 2].

Hypothyroidism was present in only one person per group, or 3.33% of the subjects in each group. The differences were statistically insignificant because the p-value was more than 0.05. Six smokers in group A and five in group B, or 20% and 16.67% of the total study population, respectively, were smokers. The differences were statistically insignificant because the p-value was more than 0.05. When hypertension was considered a risk factor, the highest percentage was noted. Thirteen of the thirty subjects in group B (43.33%) and eleven of the thirty subjects in group A (36.67%) had hypertension. The values, the p-value came out to be 0.76 (>0.05), making the difference between both the groups statistically non-significant as shown in [Table 3].

Table 1: Age and Gender distribution among the study groups.

Age Group (in years)/ Gender	Group A (G)		Group B (G+V)		p-value
	N	%	N	%	
18-30	2	6.67	1	3.33	0.13
31-40	6	20	5	16.67	
41-50	10	33.33	8	26.67	
>50	12	40	16	53.33	
Male	17	56.67	18	60	0.72
Female	13	43.33	12	40	

Table 2: BMI among the study groups

Group	Mean	SD
Group A (G)	27.01	4.24
Group B (G+V)	27.69	3.93
t-test	1.77	
p-value	0.45	

Table 3: Risk factors among the study groups

Factors	Group A (G)		Group B (G+V)		p-value
	N	%	N	%	
Smoking	6	20	5	16.67	0.91
Hypertension	11	36.67	13	43.33	0.76
Hypothyroidism	1	3.33	1	3.33	1

Table 4: Comparison of NRS scale among the study groups

Interval	Group A (G)		Group B (G+V)		p-value
	Mean	SD	Mean	SD	
Baseline	7.93	3.40	8.08	2.96	0.77
30 Days	6.06	1.37	5.92	2.05	0.61
Last Followup (3 months)	4.49	0.85	3.97	1.29	0.08
Mean Difference (Baseline-Last Followup)	3.44	1.81	4.11	1.94	0.047*

Table 5: Adverse effects among the study groups

Variables	Group A (G)		Group B (G+V)		p-value
	N	%	N	%	
Constipation	4	13.33	2	6.67	0.08
Orthostatic Hypotension	3	10	1	3.3	
Lethargy	3	10	1	3.3	
Decreased Appetite	2	6.67	1	3.3	

At baseline, mean NRS score was comparable in group A (7.93 ± 3.40) and B (8.08 ± 2.96) but there was no statistically significant difference among the two groups as p-value > 0.05. After 30 days of respective treatment, NRS score decreased in both the groups (6.06 ± 1.37 in group A and 5.92 ± 2.05 in group B) but more decrease was seen in group B as compared to group A, though no statistically significant difference was reported (p-value > 0.05).

At the end of 3 months i.e., last follow up,further decrease in NRS score in both the groups (4.49 ± 0.85 in group A and 3.97 ± 1.29 in group B) were reported with more decrease in group B but upon comparing the results , no statistically significant difference was found (p-value > 0.05) between groups A and B. The NRS scales in the two groups from the baseline to the final follow-up day, we found the biggest difference. Group A's NRS score was 3.44 ± 1.81, while group

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B's score was 4.11 ± 1.94. These results show that both groups' NRS scales dramatically dropped from the baseline to the end of our 3-month follow-up period. Thus, both groups experienced a decrease in pain. with a statistically significant difference as a p-value < 0.05, group B which received both gabapentin and vitamin C experienced a statistically significant decrease in pain than group A which received gabapentin alone as the p-value was < 0.05 (0.047) as shown in [Table 4, Figure 1].

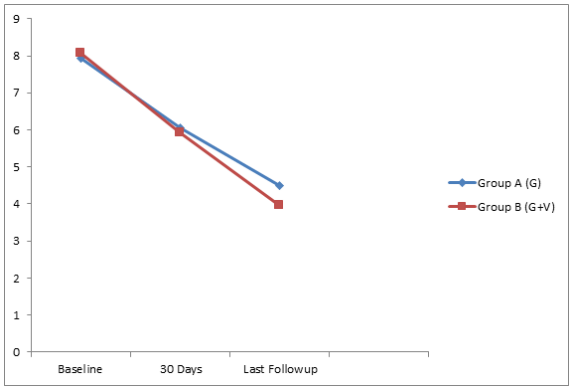

Figure 1: Comparison of NRS scale among the study group

In statistical terms, constipation was the main adverse impact observed in both groups. In group A, 4 out of 30 subjects and in group B, 2 out of 30 subjects complained of this. Three individuals in group A and one patient in group B experienced orthostatic hypotension, a well-known side effect of gabapentin. Lethargy was reported by 3 patients in group A and 1 patient in group B during our investigation. Throughout our investigation, two patients from group A and one from group B reported having less hunger. There was no statistically significant difference between the two groups, despite the fact that group B experienced fewer adverse effects overall than group A (p-value > 0.05).

DISCUSSION

Neuropathic pain is a painful condition that arises after a lesion or an insult to the somatosensory nervous system, either in the central or peripheral location.[16] It affects 7%-10% of the general population, producing a spontaneous ongoing shooting or an evoked pain after a noxious or non-noxious stimulus.[17] Long-term complications of neuropathic pain depend upon the underlying pathology, but in general, if the symptoms persist for long they tend to become chronic and respond less to analgesics. Psychosocial symptoms like depression, anxiety and sleep disturbances are frequently observed with chronic neuropathic pain followed by physical disability and poor quality of life (QOL).[16] Pharmacological therapy is worldwide used as the first line of management of neuropathic pain, followed by interventional strategies, such as nerve blocks and neuromodulators.[18] Antidepressants and antiepileptics have been the most studied drugs in neuropathic pain, including those with confirmed efficacy, like amitriptyline and serotonin-noradrenaline reuptake inhibitors. Various such traditional treatments have been used to improve the QOL of the patients having neuropathic pain, but more than two-thirds of them have obtained insufficient pain relief.[4]

Controlled trials have been conducted on recent advancements in medicine to investigate the effect of vitamin C in the treatment of neuropathic pain, especially post-herpetic neuralgia and cancer-related neuropathy.[19,20] The analgesic mechanism of vitamin C owes to its antioxidant and anti-inflammatory properties.[21] It is found to increase the synthesis of catecholamine, dopamine and act as a co-factor for the synthesis of nor-epinephrine, all of which have a significant role in pain relief.[22]

The present hospital based observational study was conducted among 60 patients of Neuropathic pain in the Department of Anaesthesiology and Critical Care, Muzaffarnagar Medical College. Patients were equally distributed into group A (prescribed only gabapentin in the dosage of 10 mg/kg) and B prescribed gabapentin (10mg/kg) and vitamin C in the dosage of 10 mg/kg as an adjunct to gabapentin). Males were comparatively more as compared to female in both the study groups. To support our study, Rowbotham M et al,[23] in their study in the year 1998 also revealed that males were comparatively more affected with neuropathic pain than females. They did a randomized controlled trial that evaluated the efficacy and safety of gabapentin in reducing postherpetic neuralgia (PHN) pain. The trial included 229 subjects who were randomized to receive either gabapentin or placebo out of which the majority population were males (118). In 2021, Amerta Bai et al,[24] in their reported similar male dominance as observed in our study. Males are, in general, more prone for having neuropathic pain as compared to females though the difference in both the groups came out to be statistically insignificant.

Maximum subjects were from age group of >50 years followed by 41-50 year age group. Minimum subjects were from age group of 18-30 years. When age distribution was compared among the study groups using chi-square test, we found out that age distribution was comparable among both the groups but there was no statistically significant difference was found in this study (p-value was more than 0.05). Hassanzadeh et al,[25] conducted a study in 2023 named also found that the mean and standard deviation of the age was equal to 50.20 ± 7.44 and 50.47 ± 7.57 respectively in both the groups. People of age groups 50s and 60s are more prone to getting affected by neuropathic pain, be it due to more incidences of trauma and degenerative changes in theses age groups.

BMI in group A was 27.01 ± 4024 and 27.69 ± 3.93 kg/m2 in group B with a p-value of 0.45. This brought us to the conclusion that there were no statistically significant difference when BMI was

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compared in both the groups. Jun Hozumi et al,[26] in the year 2016 studied on concluded that obesity is strongly associated with increased pain severity and prevalence in various conditions such as knee osteoarthritis, postoperative pain, headaches, shoulder pain, fibromyalgia, peripheral neuropathy, chronic pain, and neuropathic pain and that obesity may aggravate neuropathic pain, particularly paroxysmal pain, possibly due to obesity-associated inflammation. Overall, their findings support the notion that obesity is a significant risk factor for the development and exacerbation of various pain conditions. However our study showed no statistically significant difference between BMI and occurrence of neuropathic pain possibly because of less diverse sample size and population. It opens up the room for conductance of further studies to establish a direct relation between BMI and neuropathic pain.

Just 1 participant (3.33% of the subjects) in each group had hypothyroidism. 20% of the study population were smokers. 36.67% of patients in group A and 43.33% in group B had hypertension. Comparison of groups showed non-significant results. Malgorzata Monika Brzozowska et al,[27] in 2021 highlighted the potential for severe neuromuscular consequences from advanced and chronic autoimmune hypothyroidism, emphasizing the importance of early diagnosis and management. Although we did not find any co-relation between hypothyroidism and neuropathic pain, probably because of small sample size. Thus, we can say that hypothyroidism is not an independent risk factor for the development of neuropathic pain. Sercan Bulut Celik et al,[28] in their study in 2017 concluded that smoking is a risk factor for neuropathic pain and the possibility of neuropathic pain increases as the duration of smoking and addiction level increase. Emanuel Schembri et al,[29] in 2021 also found out that current smoking status and a higher nicotine dependence were both independently associated with an increased risk for chronic low back pain and/or chronic radicular neuropathic pain. Our study is not coherent with any of the above studies because our study does not reveal any statistically significant difference among both the study groups in terms of smoking and development of neuropathic pain but there is a possibility of development of neuropathic pain in smokers because it is an established fact that smoking causes neuritis (inflammation of nerves) and secondary to it, may lead to neuropathy. To establish this co-relation, further studies needs to be done on a larger population as our less sample size might not have been sufficient enough for drawing the link between smoking and development of neuropathic pain. A study done by Georgios Ponirakis,[30] in 2019 investigated the association between hypertension and diabetic peripheral neuropathy (DPN) in individuals with type 1 diabetes mellitus (T1DM). The study found that hypertension was an independent risk factor for neuropathy development in type-1 diabetes mellitus patients. This finding was slightly different from our study in respect to that we did not find any statistically significant difference between groups' A and B. It might be because our sample size was less and also because we did not include diabetic patients in our study.

Groups A (7.93 ± 3.40) and B (8.08 ± 2.96) had similar mean NRS scores at baseline. Both groups experienced a drop in NRS scores after 30 days of treatment. Though there was a considerable fall in NRS in both the groups with group B experiencing a greater decrease (8.08 to 5.92) in NRS than group A (7.93 to 6.06). After three months, or the last follow-up, both groups' NRS scores decreased further, with group B experiencing a greater decrease. The largest change was observed when we compared the NRS scales across the two groups from the baseline to the last follow-up day (group A: 7.93 to 4.49 and group B: 8.08 to 3.97). On applying student's t-test, we found that there was statistically significant decrease in pain score in group B as compared to group A (p-value = 0.047) which is less than 0.05. In 2021, Majid Davari et al,[31] carried out a systematic review and meta-analysis concluded that, PGB and GBP came out to be equally effective in treating neuropathic pain associated with spinal cord injury.Philip J Wiffen et al,[32] in the year 2017 did a study also reveals the same that gabapentin is effective for the treatment of neuropathic pain.A prospective study conducted in 2007 by Chang Hwan Yeom, Gyou Chul Jung, and Keun Jeong Song,[33] found that taking vitamin C levels for one to four weeks could reduce pain in people with advanced cancer. Hidenori Takahashi, Haruyoshi Mizuno, and Atsuo Yanagisawa,[34] in the year 2012 also reveals the same beneficial effect of vitC on quality of life in cancer patients. Similarly, in a study conducted by Martin Schencking et al,[19] in 2012 found that after taking vitamin C, herpes zoster patients saw a significant reduction in pain. Rui Li, Le Shen, Xuerong Yu, Chao Ma and Yuguang Huang,[14] in 2016 verified that Vitamin C can increase Gap's analgesic effects for nerve damage, perhaps enabling a decrease in the drug's effective dosage. Thus, our study shows coherence with the past studies done as stated above and so we can conclude that gabapentin is an established drug in neuropathic pain. But no direct study has been done in the past which compares the efficacy of gabapentin and vitC over gabapentin alone in the treatment of neuropathic pain. Our investigation revealed that vitamin C has a tendency to shield tissues and cells from oxidative damage. It is thought to be a strong antioxidant that is capable of eliminating many different types of reactive oxygen species. Its well-known oxidative stress features lead to the assumption that it acts under oxidative stress circumstances. In addition, it possesses anti-inflammatory qualities and serves as a cofactor in the body's manufacture of catecholamine neurotransmitters, emphasizing its involvement in neuromodulation. Therefore, a combination of gabapentin and vitC is better than gabapentin alone

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in the treatment of neuropathic pain as the combination significantly improves the pain score.

But because our study is a pilot study, not having a backup study and done on a lesser population of patients, there is a whole room open up for doing further studies on the combination of gabapentin and vitC in patients of neuropathic pain.

The most commonly seen established adverse effects of gabapentin are orthostatic hypotension, dizziness, somnolence, lethargy, decreased appetite and constipation. Among these constipation, orthostatic hypotension, lethargy and decreased appetite were revealed among the study groups. Muhammad Nabeel Ghayur,[35] in his case report in the year 2021 documented the potential adverse consequences of combination therapy with gabapentin and pregabalin. he emphasized upon the potential adverse effects of these medications has led to an increase in adverse effects of these drugs such as drowsiness, dizziness, fatigue, and ataxia and the importance of responsible prescribing, efficient checking of medication profiles, and timely follow-up to ensure patient safety. Similarly In 2021, Amerta Bai et al,[24] revealed that the most common adverse event in both groups was constipation, followed by orthostatic hypotension. There was no significant difference in adverse events between both groups. Other studies showed similar results in accordance to our study.[36-40]

Limitations: First, since the study was conducted in a single institute, the sample size was less diverse. Second, participants' compliance with medication was not monitored, which might have impacted the result. Also as the present study is one of the rarest to compare vitamin C in combination with Gabapentin and compared to Gabapentin alone in neuropathic pain, so we were not able to compare the results with previous studies. Therefore, we can't state that the results of the present study can be generalized, therefore further studies were required to approve the efficacy of vitamin C in combination with Gabapentin in neuropathic pain.

CONCLUSION

One of this trial's strengths is that it shows that vitamin C have a synergistic effect in combination with gabapentin in Neuropathic Pain treatment. Hence this study manifested that combined therapy with Gabapentin and vitamin C is more effective as compared to monotherapy with gabapentin. Moreover, vitamin C is cost-effective and appears to be a safe adjuvant therapy for neuropathic pain relief. Patients should be encouraged to take vitamin C along with pharmacological management to get maximum relief from pain. Furthermore, this combination is safe with minimal side effects and as such tolerated well by the patients.

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